UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,447	11/13/2003	Gattadahalli M. Anantharamiah	21085.0143U2	8707

23859 7590 05/31/2006

NEEDLE & ROSENBERG, P.C.
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,447	ANANTHARAMIAH ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *9-13 and 18-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-34* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/7/05, 3/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and amendments filed 16 March 2006 have been entered. Claims 1 – 34 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group I and SEQ ID NO:5 as the specific sequence in the reply filed on 16 March 2006 is acknowledged. The traversal is on the ground(s) that search of all five inventions, and all 207 sequences recited in original claim 4, would not overly burden the examiner. This is not found persuasive for the following reasons:

1) With respect to applicant's argument that search and consideration of all five inventions together would not overly burden the examiner, applicant is respectfully reminded that pp. 2 – 5 of the restriction requirement mailed 16 February 2006 did in fact set forth the reasons why a) each invention is independent and distinct from one another and b) why search for any one of the inventions would not be informative as to the novelty or non-obviousness of any other invention. Applicant did not traverse the examiner's assertions that the inventions are distinct. With respect to the search burden, the instantly-elected invention is a polypeptide. Search for this invention requires a thorough search of the patent literature, non-patent literature, and the protein databases to determine if the claimed invention, or an obvious variant thereof, has been disclosed in the prior art. No search for an antibody is required, nor is a search for a nucleic acid. Searching for the specific method steps of Group IV are not required, and search for transgenic animals is not required. In fact, searching for nucleic acids would not be informative as to whether or not the claimed invention, a protein, is novel. Searching for a transgenic animal would not be informative as to the novelty of the claimed invention, which is not an animal but "a synthetic apolipoprotein-E mimicking polypeptide" (see claim 1). Thus because the searches required for the five different groups are divergent, the examiner would have to undertake multiple additional searches in order to search all five inventions at once.

2) With respect to applicant's argument that search and consideration of more than one sequence is not overly burdensome, applicant is reminder that absent evidence to the contrary, each amino acid sequence is assumed to be an independent and distinct invention (see MPEP § 803.04. Although the text of that section is on point to nucleic acid sequence which encode different amino acid sequences, the same logic applies to the amino acid sequences themselves). Search of any one sequence will not reveal if another sequence is novel, so each

SEQ ID NO: must be searched independently. Searching more than one sequence would be burdensome not only on the examiner, but also on the USPTO's limited computer resources. Additionally, the generic structure recited in claim 1, i.e. SEQ ID NO:210, only explicitly recites four amino acid residues and this minimally recited structure is not sufficient to impart a common utility to all members of the genus, as explained in further detail in the rejection under 35 USC 112, first paragraph below. Since SEQ ID NO:210 does not properly link all sequences, rejoinder of additional sequences is not appropriate at this time.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 9 – 13 and 18 – 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 16 March 2006.

4. Claims 1 – 8 and 14 – 17 are under examination.

Claim Objections

5. Claim 4 is objected to because of the following informalities: it recites multiple sequences identifiers which refer to identical sequences. For example, SEQ ID NO:s, 5, 8, 10, and 13 are all identical to one another. SEQ ID NO:2 has the same sequence, but requires that the C-terminus be amidated. However this is explicitly required by claim 1, so SEQ ID NO:2 is also identical to SEQ ID NO:5,8,10, and 13. SEQ ID NO:s 115 and 116 are identical to one another. Applicant is required to carefully review the sequences claimed to ensure that each sequence is only claimed once in any given claim. Furthermore, claim 4 recites non-elected subject matter, specifically SEQ ID NOs:2, 4, 8, 10-11, 13, 18, 21,110-121, 127, 129, 131, 133, 137, 141, 145, 150, 155-160, 167, 168, 194-196, 203-204. Appropriate correction is required.

6. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7 is limited to "synthetic" embodiments of claim 1, but claim 1 requires that the polypeptide be synthetic (see claim 1, first line).

7. Claim 16 is objected to because of the following informalities: it recites "claims 1", which is grammatically incorrect. Appropriate correction is required.

35 USC § 101

8. Utility is acknowledged for the claimed invention. The specification asserts that the claimed invention is useful for lowering cholesterol. SEQ ID NO:210 is a generic sequence; SEQ ID NO:2 falls within the scope of the generic sequence; SEQ ID NO:5 is identical except that it is not amidated at the C-terminus. The specification discloses that SEQ ID NO:2 is also called "R-18L" (see page 50 lines 24 – 26), and that "R-18L" peptide lowers cholesterol level *in vivo* in ApoE(-) mice (see Example 5, p. 57). Thus the specification discloses a specific and substantial asserted utility for at least one species falling within the scope of generic claim 1.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 – 4, 6 – 8, 14 – 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising SEQ ID NO:5, does not reasonably provide enablement for the broad genus of polypeptides as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

In the instant case the nature of the invention is complex. Claim 1 allows for a very large number of permutations within the core sequence, only four residues are explicitly recited within SEQ ID NO:1. The art teaches that the substitution of amino acid residues is complex and the effects on protein function are not easily predicted. See for example Weers et al. (2001.

European Journal of Biochemistry 268:3728-3735), who teach that small mutations in the apolipoprotein E molecule lead to changes in its shape, and that these changes in shape (tertiary structure) influence the ability of the protein to form bind with lipids and thereby change its physiological function (see p. 3734, first column). Furthermore Zaiou et al. (2000. Journal of Lipid Research 41:1087-1095, cited on IDS filed 2 March 2006) teach that maintaining a helical structure within residues 140 – 150 of Apo-E is crucial to allow receptor binding (see p. 1093, first column). Given the unpredictable effects of changes to the amino acid on protein shape and function, the skilled artisan would have to resort to a very large degree of experimentation to determine how to use the entire genus of compounds encompassed by claim 1. The generic nature of the structure recited in claim 1, combined with the lack of any required function, gives the claimed invention very broad scope. The structures which are explicitly recited, namely four arginine residues, do not provide sufficient structure to define the genus.

The claims are very broad. With the exception of claim 4, which recites a plethora of SEQ ID NOs, many of which are non-elected, and claim 5, drawn to SEQ ID NO:5, they allow for a very large number of substitutions within the generic sequence of SEQ ID NO:210. Only claim 14 and 15 recite any function; as the base claim is necessarily broader than any dependent claim, claim 1 encompasses proteins which neither enhance binding to, nor enhance degradation of, LDL or VLDL. The specification does not teach the artisan how to use proteins which do not enhance degradation of LDL or VLDL. There is no evidence that the generic structure of SEQ ID NO:210 imparts any particular function common to all members of the genus

Given the breadth of the claims, the large number of embodiments contained within the scope of the claims which the specification does not teach how to use, and the lack of guidance in the unpredictable nature of the effects of amino acid substitution on protein structure, and therefore function, it would take undue experimentation on the part of a skilled artisan to make and use the claimed invention commensurate in scope with the claims.

10. Claims 1 – 8 and 14 – 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses several sequences which fall within the scope of the structure of SEQ ID NO:210. These include the sequences recited in claim 4, however note that many of these sequences are identical to one another (for example SEQ ID NO:5,8,10,13 are identical; SEQ ID NO:2 differs only by inclusion of an amide at the C-terminus, although this is required by claim 1; SEQ ID NO:115 – 116 are identical to one another. The disclosed sequences recited in claim 4 do not indicate that applicant was in possession of the generic invention encompassed by SEQ ID NO:210. This structure has many variable residues, and allows for much more variability that what is present in the disclosed sequences. For example, the first residue may be any of glycine, threonine, serine, or alanine, but the specification only discloses sequences which begin with glycine. There is no disclosure of sequences which begin with threonine, serine, or alanine which fall within the scope of SEQ ID NO:210. Similarly, there is no disclosure of polypeptide sequences with tyrosines at the fifth position, even though this is clearly encompassed by claim 1 and dependent claim 2. The list above is exemplary, not exhaustive. Given the very large number of possible permutations of generic SEQ ID NO:210 which are not supported by actual disclosure of sequences, the specification does not provide sufficient support for the generic claim.

A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606

(Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606." While the above quotation from Fiers is on point to DNAs, the same logic applies to amino acid sequences, claimed herein. As applicant was not in possession, for example, of protein sequences encompassed by SEQ ID NO:210 that begin with anything other than glycine, or that have tyrosine in the fifth position, applicant was clearly not in possession of the claimed invention. Furthermore, the four aginines recited explicitly in SEQ ID NO:210 are not sufficient to impart a common utility to all members of the genus. For example, SEQ ID NO:2, which is one member of the genus, lowers cholesterol. However other proteins with four arginine residues spaced in the same fashion as SEQ ID NO:210, do not share this function. For example the prior art protein disclosed by Harris (US Patent 5,877,153, SEQ ID NO:10), is not disclosed as having an effect on cholesterol, but rather is a heparin-binding protein. Additionally, claim 8 clearly encompasses peptidomimetics. This term is defined on p. 16, beginning at line 20 and is clearly outside of the scope of polypeptides, as it must include "some alteration of the normal peptide chemistry". This term is very broad, and the specification does not actually disclose any peptidomimetics. There is no evidence that applicant was in possession of any peptidomimetics, and certainly was not in possession of the full genus of peptidomimetics, as the breadth of this term encompasses essentially any structure at all.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 – 8, 14 – 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language

is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1, from which all other rejected claims depend recites the broad recitations "comprising an amino acid sequence" and "wherein the polypeptide comprises", and the claim also recites "wherein the polypeptide *consists of*" which is the narrower statement of the range/limitation.

Additionally, claim 1 is indefinite because the term "domain", recited in the final line of the claim, is a variable term whose meaning depends on context, as well as one's own understanding of what a "domain" is. An immunologist may consider a very few amino acids to be a domain appropriate for eliciting an antibody-producing response by a host animal, whereas a protein biochemist might consider a phosphorylation site to be a domain, and one who studies ligand-receptor interaction might consider a much larger portion of a molecule to be a domain, such as an extracellular domain.

Claim 3 is further indefinite because it recites the limitation "wherein the polypeptide comprises about 10 to about 30". Because the claim uses both open and relative language (i.e., "comprising" and "about") it is not possible to determine the metes and bounds of the claim.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 – 4, 6 – 8, and 14 – 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris et al. (US Patent 5,877,153, issued 2 March 1999).

Claim 1 does not require the full-length sequence set forth as SEQ ID NO:210, but rather only requires "an amino acid sequence". This language is sufficiently broad to encompass fragments of the sequence as small as two amino acids.

Harris teaches SEQ ID NO:10, which comprises arginines at residues 5, 6, 13, and 16. These correspond to the arginines at residues 3, 4, 11, and 14 of applicant's SEQ ID NO:210 (see enclosed alignment). As the reference sequence comprises at least two consecutive

residues of the claimed sequence, it is "an amino acid sequence", as recited in claim 1. The Harris reference also teaches that peptides are to be acetylated at the N-terminus and amidated at the C-terminus (see column 19 lines 20 – 24), as recited in claim 1. Claim 2 is rejected because even though it recites specific hydrophobic residues, the breadth of the claim still allows for "an amino acid sequence" as explained above. Harris's sequence is 19 amino acids long, and thus is within the scope of claim 3. Claim 4 recites SEQ ID NO:5 and allows for "a sequence of consecutive amino acids", and since the sequence from Harris has two consecutive arginine residues, as does SEQ ID NO:5, the prior art reference anticipates the invention of claim 4. Claim 6 is limited to recombinant polypeptides, and while the Harris reference does not explicitly teach recombinant polypeptides, this is a product-by-process limitation which does not distinguish the claimed product from the prior art product. The polypeptide is the same whether it is purified from a source or produced recombinantly or by any other manner such as synthesis, thus the reference anticipates claims 6 and 7. Harris also teaches synthesis of the product with D-amino acids (see column 19 lines 54 – 58) and as this is clearly encompassed by applicant's definition of peptidomimetic on p. 16 of the specification, the Harris reference anticipates claim 8. Claims 14 – 15 are limited to specific polypeptides with certain properties. The Harris reference is silent as to whether or not the disclosed products have these properties. However as the structural limitations of the claims are anticipated by the reference, claims to the inherent properties are also anticipated as a product and its properties are inseparable. Harris teaches compositions comprising the polypeptide and carriers such as saline (column 7 line 27 – 30), which is sufficient to meet the limitations of claim 16. Harris teaches that the pharmaceutical carriers are to be "acceptable" (column 6 line 18), and specifically teaches that phosphate buffer is acceptable as the activity of the compounds are maintained in this buffer (see column 11 line 45 for example). Harris clearly contemplated phosphate buffers and saline to both be pharmaceutically acceptable and thus the reference anticipates claim 17 as well.

Conclusion

13. No claim is allowed.

14. Claim 5 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Daniel E. Kolker, Ph.D.
May 30, 2006

JANET L. ANDRES
SUPERVISORY PATENT EX